Review Article

Peri-transplant management of nonalcoholic fatty liver disease in liver transplant candidates

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Abstract: The incidence of non-alcoholic fatty liver disease (NAFLD) is rapidly growing, affecting 25% of the world population. Non-alcoholic steatohepatitis (NASH) is the most severe form of NAFLD and affects 1.5% to 6.5% of the world population. Its rising incidence will make end-stage liver disease (ESLD) due to NASH the number one indication for liver transplantation (LT) in the next 10 to 20 years, overtaking Hepatitis C. Patients with NASH also have a high prevalence of associated comorbidities such as type 2 diabetes, obesity, metabolic syndrome, cardiovascular disease, and chronic kidney disease (CKD), which must be adequately managed during the peritransplant period for optimal post-transplant outcomes. The focus of this review article is to provide a comprehensive overview of the unique challenges these patients present in the peritransplant period, which comprises the pre-transplant, intraoperative, and immediate postoperative periods.

Keywords: Liver transplant; peri-transplant management; non-alcoholic fatty liver disease (NAFLD); non-alcoholic steatohepatitis (NASH); cirrhosis

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Nonalcoholic steatohepatitis (NASH) is currently the second leading cause for liver transplantation (LT) waitlist registration/liver transplantation overall, and in females, the leading cause. It is projected that NASH will likely rise to become the leading indication for LT in males as well (1). According to the United Network for Organ Sharing and Organ Procurement and Transplantation Network data, there was a 162% increase in LT secondary to NASH from 2003 to 2014 (2). NASH cirrhosis is the most rapidly growing indication for ACLF-related hospitalization and use of hospital resources (3). ACLF increased by 24% between 2006 and 2014 with a 63% increase in nonalcoholic steatohepatitis (NASH) cirrhosis (3.5% to 5.7%); a 28% increase in patients with alcoholic cirrhosis (5.6% to 7.2%); a 25% increase in patients with other etiologies (5.2% to 6.5%); and no significant change in patients with viral hepatitis (4.0% to 4.1%) (3). NASH as a cause of LT related to hepatocellular carcinoma (HCC), increased from 8.3% in 2002 to 10.3% in 2007 to 13.5% in 2012. The number of patients undergoing LT for HCC secondary to NASH increased by nearly 4-fold from 2002–2012 (4). NASH patients requiring LT were older and waitlist mortality was higher compared to patients with other etiologies of chronic liver disease (5). Dulai *et al.* did a systematic review and meta-analysis of 5 studies. Cumulative incidence of death within 3 years of listing for LT was 29% in NASH (6).

Table 1 Summary of early post-LT mortality across various studies in NASH patients *vs.* non-NASH patients

Study	Year	NASH survival (%)				Non-NASH survival (%)			
		Patients (N)	30-day	90-day	1 year	Patients (N)	30-day	90-day	1 year
Haldar *et al*. (10)	2019	1,667	–	–	84.1	48,206	–	–	86.3
Agopian *et al*. (11)	2012	144	–	90	84	1,150	–	93	81
Kennedy *et al*. (12)	2012	129	–	–	90	775	–	–	92
Vanwagner *et al*.* (13)	2012	115	–	–	81.3	127	–	–	88.1
Afzali *et al*.** (14)	2011	1,810	–	–	87.6	–	–	–	–
Barritt *et al*. (15)	2011	21	80.9	–	76.2	97	97	–	83.5
Charlton *et al*. (16)	2011	1,959	–	–	84	33,971	–	–	87
Yalamanchili *et al*. (17)***	2010	18	–	–	85.6	1,795	–	–	86.3
Malik *et al*. (18)	2009	98	95.9	–	78.6	686	95.8	–	84.8
Bhagat *et al*. (19)	2009	71	–	–	82	83	–	–	92

*, alcohol-induced liver disease – NASH patients more likely to die from adverse CV event; predicted by prolonged QT interval; **, authors concluded that NASH patients more likely to die from CV complications. Risk factors were old age and obesity; ***, authors concluded that NASH patients are more likely to die from CV disease.

Factors such as poor performance status, encephalopathy, diabetes, high MELD score, Hispanic race, older age, and a low serum albumin were the main causes of death in patients with NASH who were on the waitlist for LT (7).

NASH is considered as the hepatic manifestation of metabolic syndrome, and as such, the constellation of comorbidities such as diabetes, hypertension, dyslipidemia, and obesity are significantly common in these patients (8). In addition, complications related to these comorbidities such as chronic kidney disease (CKD) and coronary artery disease (CAD) are quite common in NASH patients, and their increased prevalence puts significant clinical challenges in the management of NASH patients on the LT wait-list and during the peritransplant period (9). In this review, we have described these complex challenges in the management of NASH patients with end stage liver disease and attempted to guide clinicians to best manage and prevent future complications with early interventions.

Risk factors affecting graft and patient survival in NASH

Recent meta-analysis of 9 studies showed survival of patients at 1, 3, and 5 years after liver transplantation was similar to other chronic liver disease. Studies that have compared mortality following LT in patients with NASH to post-LT patients with Non-NASH cirrhosis (10-19) are summarized in *Table 1*. There are unique challenges faced by patients with NASH undergoing LT, a summary of those as well as guideline-based management in the peri-transplant period are summarized in *Table 2* (20-38). Patients with NASH are more likely to die from cardiovascular complications or sepsis (39). While some studies showed NASH did not affect graft survival (19), other studies have shown a negative impact of NASH on graft survival, primarily due to underlying metabolic factors (15). Factors including age >60 years, BMI ≥30 kg/m^2, pretransplant HTN, and T2DM, have led to increased 30-day and 1-year mortality (18). Both obese patients with BMI more than 40 and underweight patients with BMI less than 18 are associated with increased risk of infectious complications and death (40). Beckman *et al*. did a meta-analysis of 37 studies and proved the negative effect of obesity on LT outcomes. Patients with BMI >30 had worse patient survival (72.6% and 69.8%) and graft survival (75.8% and 85.4%) than those with normal weight (41). Obesity and type 2 diabetes concomitantly increased 30-day postoperative event rate, length of hospital stay and decreased graft survival (42). Usually post-transplant diabetes can develop within 6–12 months after surgery and these patients have increased rejection and worse survival (43). Close management of the components of metabolic syndrome is crucial to long-term survival and may combat the adverse effects of immunosuppression, improving

Table 2 Unique challenges in peri-transplant period for NASH patients with reference to guidelines

Peri transplant challenge	Impact on morbidity and mortality	Guideline recommendations
Obesity and metabolic syndrome	● Increased primary graft nonfunction, and decreased survival at 30 days, 1-, and 2-year follow-up in morbidly obese patients undergoing LT (20)	● AASLD considers morbid obesity [body mass index (BMI) ≥40 kg/m^2] as a relative contraindication for liver transplantation, since these patients seem to be exposed to a higher risk of post-transplant complications and mortality (21)
	● Increased mortality risk and higher early postoperative complications, mainly due to cardiopulmonary complications in post-LT period (22)	● EASL practice guidelines state that a multidisciplinary team should carefully evaluate patients with a BMI >35 before being included in the waiting list (23)
Diabetes	● Pretransplant diabetes is associated with inferior post-operative outcomes and increased resource utilization after liver transplantation (24)	● Not enough of evidence to make recommendations for management of diabetes in early stages of cirrhosis (25)
Intraoperative hyperglycemia	● Hyperglycemia increases risk of postoperative infection and mortality (26)	● Not available
Cardiovascular disease	● Mortality due to coronary artery disease and cerebrovascular disease is highest among patients with NASH within first year of liver transplantation compared to other liver disease etiologies (27)	● ACC/AHA recommends coronary revascularization prior to liver transplant in candidates with severe CAD; bare metal stenting is the chosen approach
	● Occurrence of a cardiovascular event perioperatively associated with increased overall mortality (28)	● In patients with nonobstructive CAD, medical management with beta blockers and statins is suggested
		● AASLD recommends NASH patients should careful evaluation of identifying CVD during the transplant evaluation process (29). See *Figure 1* for an algorithm
Acute kidney injury	● Post-LT acute kidney injury associated with increased mortality and graft failure (30)	● Not available
Chronic kidney disease	● In patients with NASH, CKD was associated with increased overall mortality (31)	● Not available
	● Pre-transplant renal impairment along with diabetes is a predictor for increased post-liver transplant cardiovascular disease mortality (32)	
Sarcopenia	● Sarcopenia increases risk for delisting and death (33)	● ESPEN recommends a target intake of 35–40 kcal/kg/day and 1.2–1.5 g/kg/day of protein (34)
	● Sarcopenia is associated with post-LT infectious complications and sepsis-related mortality (35)	
Portal vein thrombosis	● PVT decreases post-LT graft and patient survival (36)	● Not available
	● No impact on waitlist mortality (37)	
	● Independent risk factor for 90-day mortality (38)	

PVT, portal venous thrombosis.

graft survival and decreasing rates of sepsis. Patients with NASH are known to have poor performance status, which has been linked to decreased graft survival and overall patient 5-year survival rates when compared with the other groups after adjusting for demographic and disease complication factors (44). African American donors are shown to have an increased risk of liver graft loss by 21.5%. When both donor and recipient were African American, graft loss increased by 36.6% (45). Optimization of obesity, hypertension, hyperlipidemia, pre-transplant cardiovascular disease, and smoking status are important in decreasing graft loss in NASH patients.

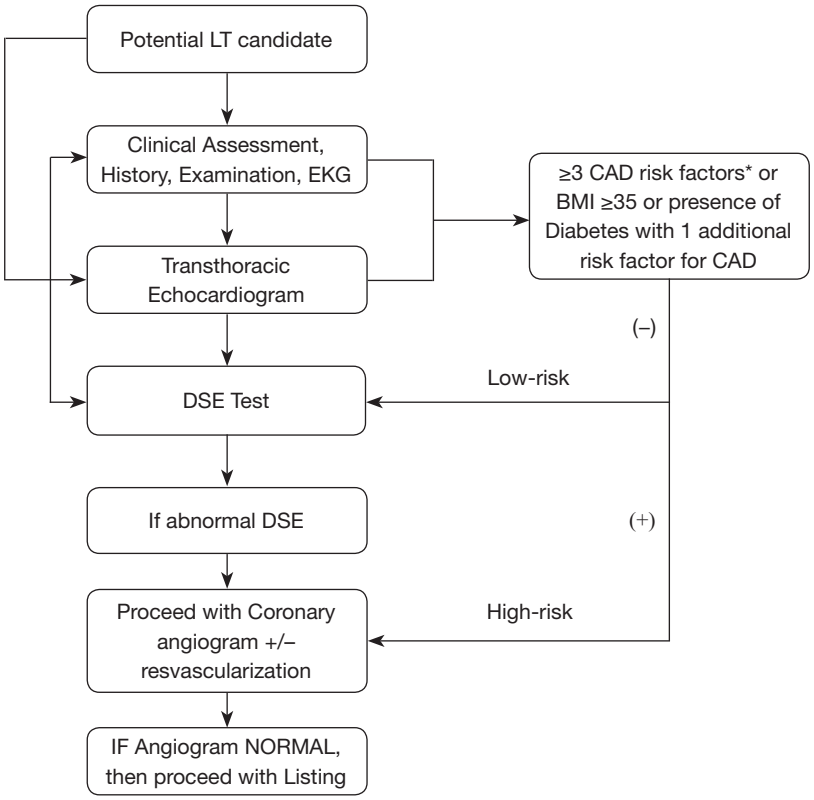

Figure 1 An algorithm for evaluating for cardiovascular risk in patients undergoing liver transplantation. All patients undergoing liver transplantation require a transthoracic echocardiogram, which can help determine the next steps in management. *, CAD risk factors: age (>45 years in males, >55 in females), Hx of smoking, hypertension, dyslipidemia, T2 DM, family hx of CAD, known hx of CAD). CAD, coronary artery disease; DSE, Dobutamine Stress Echocardiogram.

Donor and allocation issues

Older age, higher BMI, increased prevalence of diabetes and donation after cardiac death (DCD) are leading cause for liver nonuse (46). Miyaaki *et al*. noted that younger age of recipients and donor steatosis are risk factors for post-LT NASH (47). Zhang *et al*. conducted meta-analysis of 19 publications to estimate the effect of steatotic livers after LT and noted primary non function rate and early dysfunction rate was higher when moderate and severe steatotic liver donors were used. But graft survival rate and patient survival rate did not differ between steatotic and non steatotic liver donors (27). Recipients receiving liver with macrosteatosis are at increased risk of post reperfusion syndrome, renal dysfunction requiring continuous renal replacement therapy (RRT) following LT, and cardiac arrest compared to donors without steatosis (48). Steatotic grafts with >60% fat are generally not transplanted, while those with 30–60% fat when transplanted have been associated with poor results and should be considered as donors in the absence of other risk factors (49). However, Wong *et al*. assessed patients who received severely steatotic liver donors and proved even severely steatotic liver donors from low risk donors can be safely used (50). Non-enhanced computed tomography and contrast-enhanced CT attenuation measurements of liver is useful in evaluating steatosis in donor candidates with moderate to severe steatosis (51). Magnetic resonance proton density fat fraction (MR-PDFF) has good negative predictive value for diagnosing donor hepatic steatosis >10% in living donor LTs (52). Zheng *et al*. did meta-analysis of 8 studies and noted MR imaging and MR spectroscopy has high sensitivity and high specificity for diagnosing hepatic steatosis >10% to >30% in living liver donors (53).

Preoperative and selective intraoperative liver biopsies are proven to be specific compared to imaging studies

for assessing donor steatosis and can be considered in patients with abnormal imaging studies to evaluate the liver steatosis on donors (54). Pharmacological enhancement of intracellular lipid metabolism and defatting done during normothermic machine perfusion decreased steatosis in donor livers and reduced the inflammatory cytokines in the perfusate (55). Strategies such as shortened ischemia time, ischemic and pharmacological preconditioning of liver grafts, and the use of machine-based liver perfusion systems are used to optimize fatty liver grafts, which is necessary for deceased liver donors. In patients undergoing living donor LT, Bezafibrate (400 mg/day) for 2–8 weeks in the donors have reduced risk of liver injury in live steatotic grafts (31).

Factors affecting peritransplant outcomes in NASH patients

Obesity and metabolic syndrome

Obesity increases the risk of clinical decompensation in cirrhosis, possibly by increasing portal pressure. Sixteen weeks of diet and moderate exercise were safe and reduced body weight and portal pressure in overweight and obese patients with cirrhosis and portal hypertension (56). The impact of bariatric surgery on LT candidates was assessed by a few studies. Idriss *et al*. studied 78 adults who underwent liver transplant evaluation after bariatric surgery and noticed that when compared with controls without a history of bariatric surgery, patients with a history of bariatric surgery were more likely to be listed for LT, but a higher rate of delisting or death on the waiting list was noticed in patients with bariatric surgery secondary to malnutrition (57). Sleeve gastrectomy is shown to be a possibly safe alternative that can reduce the metabolic complications in the peritransplant period before and after LT while also decreasing the risk of malnutrition during LT and eliminating the risk of malabsorption of immunosuppressive drugs. Furthermore, sleeve gastrectomy allows for good endoscopic evaluation of varices and biliary complications (58,59).

Patients with morbid obesity had an increased length of stay in the hospital and appeared sick, which required extensive use of hospital resources (60). Obese patients are known to have an increase in mortality while on the waitlist and had decreased post-LT survival. A summary of studies comparing mortality in obese post-LT patients to non-obese post-LT patients (20,61-70,71-77) is summarized in *Table 3*. Obese patients were less likely to get LT compared to nonobese patients because of excessive post-operative risks (78). With respect to operative outcomes, patients with Class II obesity (BMI >35) or higher MELD scores transplanted for NASH had no difference in operative time, intensive care unit or hospital length of stay, or perioperative complications when compared to non-obese patients undergoing LT (63).

Studies examining survival outcomes in obese patients undergoing LT have shown conflicting results (79,80). Nair *et al*. (20) reviewed the UNOS database from 1988 through 1996 and reported increased primary graft nonfunction as well as decreased survival at 30 days, 1-, and 2-year follow-up in morbidly obese patients undergoing LT. Despite these earlier reports, Pelletier *et al*. (79) demonstrated that there was a survival benefit from transplantation not only for obese patients but also for patients at the extremes of BMI. A recent meta-analysis of 24 studies on 132,162 patients also reported increased mortality risk and higher early postoperative complications, mainly due to cardiopulmonary complications in obese patients after LT compared to the controls (22). Currently, the American Association for the Study of Liver Disease (AASLD), in accordance with the American Society of Transplantation, considers morbid obesity [body mass index (BMI) ≥40 kg/m^2] as a relative contraindication for LT, since these patients seem to be exposed to a higher risk of post-transplant complications and mortality (21). The European Association for the Study of the Liver (EASL) also highlights increased postoperative infections and increased hospital and/or intensive care unit length of stay in obese patients and the EASL practice guidelines state that a multidisciplinary team should carefully evaluate patients with a BMI >35 before being included in the waiting list (23).

A 2013 study that analyzed effectiveness of pre-transplant weight loss in obese patients requiring LT showed that 60% of the cohort gained weight to a BMI greater than 35 kg/m^2 post-transplantation (81). Pre-transplant obesity is a strong risk factor for developing post-transplant metabolic syndrome. Idowu *et al*. stated accumulation of atherogenic lipoproteins caused increased risk of de novo hepatic steatosis after liver transplant (82). Kim *et al*. noticed about 27.1% had NAFLD and 28.9% had severe steatosis. Obesity at biopsy and preexisting donor graft steatosis are important risk factors for recurrence of NASH after liver transplant (83). Specifically, patients with a BMI greater than 30 kg/m^2 are at greatest risk for developing post-transplant metabolic syndrome. A 2005 study by Richards

Table 3 Previous studies that have assessed the impact of obesity on survival in post-liver transplant patients

Study name	Period	BMI (kg/m^2)	Patient survival (%)					Other complications
			N	30-day	90-day	1 year	3-year	5-year	
Nair *et al.* (20)	1988–1996	Obese BMI <25	2,611	92		86		53	● 1-, 3-, 5-year mortality was high in severely obese (BMI >40) group compared to non-obese group
		Non obese BMI >30	8,382	94		84		56	● Intraoperative mortality was similar between groups
Boin *et al.* (61)	1991–2006	Obese BMI >30; mean BMI 34	38			61.3		51	● Postop creatinine was higher in obese group. Operative times, blood transfusion and ICU stay similar in both groups. Survival was similar in both groups
		Non obese BMI 18.5–29.9; mean BMI 24	206			68		47	
Braunfeld *et al.* (62)	1992–1996	Obese mean BMI 36.2	40	78		68			● Intraoperative and post-operative complications are same
		Non obese; mean BMI 23.4	61	86		75			● Length of surgery and transfusion requirement was same
									● Length of ICU stay and wound complications are similar
Conzen *et al.* (63)	2002–2012	Obese BMI >30	513					51.3	● Operative times, ICU stay, perioperative complications and survival at 1 and 3 years similar between both groups
		Non obese BMI 18–29.9	272					78.8	
Fujikawa *et al.* (64)	1990–2005	Obese BMI >30	167			86		71	● No differences in graft survival or patient's survival, hospital stay, operative complications
		Non obese BMI <25	288			82		67	
Hakeem *et al.* (65)	1994–2009	Obese BMI >30	145			86	78	70	● No difference in patient and graft survival noticed
		Non obese BMI 18–25	643			80	76	70	● Morbidly obese patients had increased ICU stay
									● No change in blood transfusions needed, post op complications
Hilling *et al.* (66)	1990–2003	Obese BMI >30	20	80	60	50			● Operative time, transfusions needed, ICU stay was similar between both groups
		Non obese BMI 19.1c29.3	20	90	85	80			● Mortality higher in obese group
Lamattina *et al.* (67)	1997–2008	Obese BMI >30 (35-40)	83			91	78	78	● Operative time, ICU stay, transfusions needed were higher in obese group
		Non obese BMI 18–25	216			94	86	83	
Leonard *et al.* (68)	1990–1994 and 1998–2006	Obese BMI >35	69	97		80		88	● No difference in patient and graft survival
		Non obese BMI 18.5–25	561	98		89		80	● ICU stay was similar in all groups except in class 3 obesity
Mathur *et al.* (69)	1996–2008	Obese BMI >30	58		4				● Primary graft dysfunction was similar in both groups
		Non obese BMI <25	47		3				

Table 3 (*continued*)

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Study name	Period	BMI (kg/m^2)	Patient survival (%)					Other complications
			N	30-day	90-day	1 year	3-year	5-year	
Nair *et al.* (70)	1994–1996	Obese BMI (>31.1 for men and 32.3 for women)	21			90	66		• Length of hospital stay was higher in both obese and severely obese patients • Number of blood transfusions was similar in all groups
		Non obese BMI (BMI <27.3 for men and <27.8 for women)	64			89	79		• Survival rate similar in all groups • Post-transplant complications highest in obesity group
Perez-Protto *et al.* (71)	2005–2011	Obese BMI >38	47			94	85		• ICU stay and blood transfusion needed were common between both groups
		Non obese BMI 20–26	183			78	76		• Patient and graft survival similar in both groups
Sawyer *et al.* (72)	1989–1996	Obese BMI >35	26			77			• Patient and graft survival similar between both groups
		Non obese BMI <30	202			81			• Wound infections were higher in obese groups after transplant but other long-term outcomes are similar
Schalansky *et al.* (73)	2005–2014	Obese BMI >35	8,356			92.5	84.1	78.5	• Patients with obesity are at increased risk of mortality compared to normal weight patients
		Non obese BMI <30	969			92.2	84.4	78.8	
Singal *et al.* (74)	1988–2011	Obese BMI>35	22			96			• Patient and graft survival at 1 year similar between 2 groups
		Non obese BMI 18.5–24.9	79			89			
Werneck *et al.* (75)	2007–2009	Obese BMI >30	32			75			• Patient survival and ICU stay similar between both groups
		Non obese BMI 18.5–24.99	46			91			
Bhambha *et al.* (76)	2002–2011	Obese BMI>35	4062		94	88			• Patient and graft survival were similar in both groups
		Non obese BMI 18.5-24.9	13,262		95	88			
Beal *et al.* (77)	2003–2013	Obese BMI >30	17,339	96		92		90	• Patient mortality more in obese group
		Non obese BMI <30	34,217	97		91		89	

et al. shows that the greatest weight gain occurs after the first 6 months following liver transplant; dietary control at this point is recommended to minimize long-term morbidity and mortality resulting from obesity (84).

Diabetes mellitus

Prevalence of NAFLD is higher in patients with diabetes (85) and is also an independent risk factor for developing diabetes (86,87). Patients with diabetes and NAFLD had a higher rate of hypertension, cardiovascular disease, peripheral arterial disease, hyperlipidemia and cerebrovascular disease, and advanced fibrosis and also increased all-cause mortality, mortality related to cardiovascular disease, and liver disease related mortality (88). A recent study has also concluded that diabetes is associated with an increased risk of HCC in patients with NASH cirrhosis (89). A large national study has reported that pretransplant diabetes is associated with inferior post-operative outcomes and increased resource utilization after LT (24). Pre-transplant diabetes increased risk of portal venous thrombosis which is an independent risk factor of 90-day post-transplant mortality (38).

Management of diabetes in a cirrhotic patient awaiting LT is not without challenge. Diabetes is known to be an independent risk factor for death in liver transplant candidates (90). In cirrhotic patients, fasting glucose may be normal in up to 23% of diabetes cases, and glycated hemoglobin provides falsely low results, especially in advanced cirrhosis (91,92). Similarly, the performance of alternative glucose monitoring tests, such as fructosamine, glycosylated albumin and 1,5-anhydroglucitol, also appears to be suboptimal in chronic liver disease (91). There has been a recent trend for management of these patients by specialists (93).

In a study including 12,442 patients who underwent LT at 63 centers from 2007–2011, pretransplant diabetes was associated with inferior post-operative outcomes and increased resource utilization after LT (24). Additionally, diabetes increases the risk of developing recurrent NASH after LT (94). Machine learning techniques have identified diabetes among other important factors such as recipient age, MELD score, BMI, and dialysis before LT as the strongest predictors for 90-day postoperative mortality (95). Type 2 diabetes, hyperlipidemia, obesity, hypertension, insulin use seems to be important risk factors for the development of recurrent and de novo NAFLD (96,97). Finkenstedt *et al*. studied 237 transplant recipients and in 255 organ donors and noted that liver transplant recipients with certain genetic characteristics like patatin-like phospholipase domain-containing protein 3 (PNPLA3) is associated with an increased hepatic triglyceride accumulation and recurrence of NASH (98).

The main risk factor for post-LT diabetes is the use of immunosuppressive agents particularly the calcineurin inhibitor (CNI) family (tacrolimus and cyclosporine) (99). New-onset diabetes after transplant (NODAT) adversely affects long-term survival after LT in a manner similar to preexisting diabetes, indicating the need for more aggressive care and closer follow-up, and possibly early post-operative intervention. Sirolimus-based immunosuppression is associated with a significantly higher risk of NODAT than other immunosuppressants (100). Patients with NODAT had reduced survival and an increased incidence of sepsis and chronic renal insufficiency (101). Lastly, steroid free regimens are known to decrease diabetes, hyperlipidemia, cytomegalovirus infections but no difference in patient and graft survival, renal insufficiency, hypertension, neurological disorders and infectious complications were noted (102).

The importance of perioperative glucose control early after LT must be emphasized as the association between the immediate post-transplant glycemic control and the development of subsequent rejection has been well documented (103). Earlier studies have documented that intraoperative hyperglycemia during LT was associated with an increased risk of postoperative infection and mortality (26). Management of blood glucose in the immediate postoperative period with a transition from an insulin drip to a long acting basal insulin along with prandial, rapid-acting insulin for both diabetic and non-diabetic patients was shown to significantly decrease infections up to 1 year from operation when compared to standard glycemic control (104). Aside from these well documented complications acute kidney injury (AKI) (105) and new onset diabetes after transplantation (NODAT) (106,107) have been associated with post-LT variability in glucose control. These studies highlight the importance of post-LT glycemic control to potentially prevent graft failure and complications such as infections. In addition, early peak NODAT has been reported in donor grafts received after circulatory death (DCD) recipients (within 15 days post-LT) (108). A recent meta-analysis has concluded that hyperglycemia in the perioperative period is associated with poor post-LT outcomes (109). With the rising NAFLD population worldwide the need for close monitoring of glucose levels post-LT has become even more important as more patients with diabetes being

transplanted. Additionally, these changes have resulted in more donor grafts from older patients with DM and obesity which could be more susceptible to poor outcomes from hyperglycemic stressors (110).

Patients in the immediate perioperative period after liver transplant are in hypercatabolic state where there is increased tissue breakdown but not in hyper metabolic state (111). Patients who has tendency to do uncontrolled eating and emotional eating are at increased risk of worse weight gain >14 kg immediately after liver transplant (112). Post-LT patients secondary to NASH have lower resting energy expenditure and exercise energy expenditure so they will need aggressive diet and exercise regimens to decrease risk of weight gain (113).

So patients are advised increased protein intake 1.3–2 g/kg body weight/day and maintain optimal energy 25–40 kcal/kg/day. Need to continue intake of carbohydrate—50–70% of daily calories with decreased simple sugars and lipids 10–20% of daily calories with increased MUFAs and PUFAs (114). Neto *et al*. retrospectively reviewed patients about 5 years post liver transplant who followed with multidisciplinary team including nutritionist, endocrinologist working together with surgical team after liver transplant. By adequate control of BP, hyperlipidemia and hyperglycemia, there was an improvement in HbA1c status and weight gain in this study (115). Management of diabetes in liver transplant recipients is not very different compared to pre-transplant diabetes.

Only a few prospective studies have designed interventions aimed at managing post-LT hyperglycemia, post-transplant diabetes mellitus (PTDM) and their impact on post-LT outcomes, and as such, future studies need to be designed to address these issues.

Cardiovascular disease

The prevalence of single-vessel and 3-vessel CAD is significantly higher in patients with NASH cirrhosis compared with HCV and alcoholic cirrhosis (116). Mortality due to CAD and cerebrovascular disease is highest among patients with NASH within first year of LT compared to other liver disease etiologies (117). An algorithm for guiding evaluation for LT in NASH cirrhotic patients from a cardiovascular standpoint is summarized in *Figure 1*. In general considering their predisposition for CAD a stringent cardiac evaluation is of paramount importance. A transthoracic echocardiogram is required in all patients undergoing liver transplant evaluation to assess the structural and functional capacity of the heart. If patients have more than 2 cardiac risk factors (age >50 years, hypertension, hyperlipidemia, obesity), stress testing should be performed (118). Our center performs stress testing routinely in all patients age >40 years. The two most commonly used non-invasive stress tests are either dobutamine stress echocardiography (DSE) or nuclear perfusion stress testing (SPECT). Patients undergoing DSE should discontinue any beta blocker use 48 hours prior to the procedure as it can cause a false negative result. In our center, the DSE is considered optimal if the LT candidate achieves 85% of maximal heart rate. DSE is quite accurate in diagnosing CAD in general population, but its value in predicting CAD in cirrhotic patients with decompensated has been suboptimal as many patients do not achieve the maximal target heart rate. The sensitivity, specificity, PPV, and NPV in diagnosing obstructive CAD using DSE is 13%, 85%, 22% and 75%, respectively (119). In a recent meta-analysis, the authors found that DSE, myocardial perfusion scintigraphy (MPS), and invasive coronary angiography (ICA) do not satisfactorily predict increased risk of perioperative major adverse cardiac events or all-cause mortality among cirrhotic patients listed for LT, among small and heterogenous studies, questioning the utility of these studies (120). DSE is not recommended in patients with a left bundle-branch block (LBBB) because an increase in heart rate and contractility may cause septal perfusion abnormalities (121). DSE is also contraindicated in patients with atrial fibrillation, atrial flutter, or an automatic implanted cardioverter defibrillator (AICD). In patients with these conditions, nuclear perfusion testing should be performed instead. However, recent studies have shown that noninvasive diagnostic stress tests such as DSE or nuclear perfusion stress test may yield nonspecific results in patients waiting for liver transplant compared to other patients (122). Therefore, in patients with abnormal stress testing, coronary angiography seems to be the gold standard. Additionally, complications from coronary angiography and percutaneous intervention (PCI) were low, making this a safe procedure, per a 2018 study (116). Cardiac catheterization can be safely performed in patients with end stage liver disease despite elevated INR and thrombocytopenia (123). As per ACC/AHA guidelines, coronary revascularization in candidates with severe CAD is frequently performed prior to liver transplant and bare metal stenting was the chosen approach. PCI and revascularization are required in obstructive CAD

(greater than 50% reduction in luminal diameter of major coronaries) before a patient can be considered as a potential transplant candidate. In liver transplant candidates requiring bare metal stenting, LT should be delayed by a minimum of 6 weeks (124). In patients with nonobstructive CAD, medical management with beta blockers and statins was suggested.

Intraoperatively, LT results in acute cardiovascular changes, including reduced venous return and sudden increase in peripheral vascular resistance. These are often exacerbated by hemorrhage and reperfusion syndrome, further compromising the already stressed hemodynamics. Patients with end-stage liver disease (ESLD) also have splanchnic and systemic vasodilatation secondary to activation of the renin-angiotensin-aldosterone system. These factors lead to increased flow both in pulmonary and systemic circulations with the resultant elevated pressures in the right ventricle, pulmonary artery, and left atrium in the resting state. Additionally, cirrhotic cardiomyopathy which is noted in 40–50% of cirrhotics, may present with subclinical systolic and diastolic dysfunction, and can be unmasked after LT (125). Therefore, perioperative considerations for cardiovascular disease are significant. As per Vanwagner *et al*., NASH patients were more likely to have a cardiovascular event within 1 year after LT and about 70% of events occurred in the perioperative period even after controlling for recipient age, sex, smoking status, pretransplant diabetes, cardiovascular disease, and the presence of metabolic syndrome (13).

Predictors for post-transplant cardiovascular disease are age, male sex, diabetes, hypertension, glomerular filtration rate <60 mL/minute, and pre-transplant CVD (126). Minimizing weight gain early after LT can prevent the development of metabolic syndrome and resultant cardiovascular disease (127). Severity or extent of CAD does not impact post-LT survival, if appropriately revascularized (128). Early postoperative cardiac events are associated with inferior survival in liver transplant recipients, irrespective of underlying CAD.

AKI

AKI is a frequent complication after LT. Thongprayoon *et al*. noted an overall estimated incidence rates of post-LT AKI and severe AKI requiring renal replacement therapy are 40.8% and 7.0%, respectively. There are significant associations of post-LT AKI with increased mortality and graft failure after transplantation (30) In a study including 1,270 patients 34% developed severe AKI, including 18% requiring postoperative RRT. Five factors were identified as the strongest predictors of AKI: donor and recipient BMI, DCD grafts, fresh frozen plasma requirements, and recipient warm ischemia time, leading to a range of 0-25 score points with an AUC (Area under curve) of 0.70. The AKI prediction score is a potential tool to risk stratify recipients at risk for severe post-transplant AKI, and may be of use in early switch to kidney-sparing immunosuppression and early RRT (129). Even in patients with normal preoperative renal function, AKI was a frequent complication in LT recipients and had both negative short- or long-term effects on patient outcomes, also the severity of AKI had a dose-response relationship with worse outcomes. Patients with BMI >25, prolonged inferior vena cava clamping, prolonged cold ischemia time, or post-operative RBC requirement >10 units should be paid particular attention, which may assist in achieving better clinical outcomes (130). NASH as an independent risk factor for renal dysfunction after LT (131). Additionally, recipients with preserved renal function before LT has shown a trend toward lower risk of death with a functioning graft compared with spontaneous liver and kidney transplant (SLKT) recipients and those with pretransplant severe renal dysfunction in patients with NASH. Renal-sparing immunosuppression regimens should be considered at the time of LT to reduce the development of kidney injury in NASH patients.

CKD

Prevalence of CKD ranged from 20% to 55% among patients with NAFLD compared with 5% to 30% among those without NAFLD (132,133). A meta-analysis showed that increased risk of CKD persisted in NASH patients after adjusting for diabetes (134). In patients with diabetic kidney disease, NASH is an independent risk factor for cardiovascular events (135), and in patients with NASH, CKD was associated with increased overall mortality (136). Female sex, pre-transplant CKD, and NASH are independent predictors of development of stage 3 or greater CKD after LT (137). Pre-transplant renal impairment along with diabetes is a predictor for increased post-liver transplant cardiovascular disease mortality (32).

SLKT recipients increased from 6.3% in 2002 to 19.2% in 2011 (138). Patients with preserved renal function before liver transplant were shown to have lower risk of death and increased graft survival compared to those with pre-transplant severe renal dysfunction in patients with NASH

(139). Houlihan *et al*. noted that NASH patients undergoing liver transplant had significantly low EGFR 3 months after LT compared to non-NASH patients even after adjusting for body mass index, tacrolimus levels, diabetes mellitus, hypertension, and HCC (131). Several studies show ACE inhibitors as a treatment for NASH and decreasing the risk of CKD (140-142). ACE inhibitor therapy is thought to be effective in patients with NASH by increasing insulin sensitivity, one of the main pathogenic determinants in NAFLD (134). Pentoxifylline has shown to improve liver tests and also has renal protective action (143,144). Many other drugs like fibrates, thiazolidinediones, epidermal growth factor inhibitors, nuclear factor inhibitors are being studied to improve inflammation and fibrosis related to CKD in NASH patients (145). Their utility in the post-LT period in NASH patients has not been well studied, but appears to be a reasonable strategy.

Sarcopenia and functional status

Sarcopenia is the loss of skeletal mass and associated function and is common in cirrhotic patients due to impaired protein synthesis and inability to adequately store glycogen. Undernutrition, sarcopenia and functional decline increases mortality in waitlist candidate (146). Therefore, management of sarcopenia and frailty is essential in decreasing the dropout rate in waitlist patients. Pretransplant sarcopenia is associated with poor short-term survival post-living donor LT (147). Cirrhotic patients older than 65 years are at particular risk for sarcopenia (148,149). Sarcopenia and overall functional decline in LT candidates on the waitlist has also been shown to be associated with a higher risk of delisting or mortality despite a low baseline MELD score (33). Specifically, sarcopenia is associated with post-LT infectious complications and sepsis-related mortality (35). Sarcopenia is diagnosed based on low muscle mass plus either low muscle strength or low physical performance (150). Modalities such as dual X-ray absorptiometry, bioimpedance analysis, handgrip strength, and gait speed have been used in diagnosis of sarcopenia. However, measurements using dual X-ray absorptiometry and bioimpedance analysis in cirrhotic patients specifically may be distorted by fluid retention (151). Additionally, diminished gait speed and handgrip strength may be due to underlying confusion from hepatic encephalopathy and not necessarily a result of diminished muscle mass (152). Measurement of muscle mass by MRI or CT are gold standards for measuring muscle mass in research (150). Due to multiple modalities used in diagnosing sarcopenia, current literature yields heterogeneous results on assessment of sarcopenia.

Physical activity should be assessed to estimate functional capacity. Metabolic equivalent tasks (METs) are frequently used to assess functional status because they are simple to apply based on the ability of potential recipients to carry out certain tasks. One MET is considered the resting oxygen consumption of a 40-year-old 70 kg man (153). In patients unable to perform 4 METs of work, the preoperative risk is increased (154-156). *Table 4* categorizes functional capacity based on METs. Frailty was very prevalent in liver transplant candidates and as frailty score increases waitlist mortality worsened (146). Frailty usually worsens 3 months after LT so intense exercise programs are required pre- and post-transplant to improve endurance (157). Physical activity improves frailty but physical activity was lower in patients awaiting liver transplant and was known to increase portal pressure and increase variceal bleeding (158). Also, a 12-week course of adapted physical activity has improved muscle strength, 6-min walk distance and the ventilatory threshold power in waitlist candidates (159). Supervised aerobic and resistance training is shown to improve physical conditioning and quality in post liver transplant patients (160).

Nutritional intervention should be a focus for treating sarcopenia in cirrhotic patients awaiting LT. The European Society for Parenteral and Enteral Nutrition (ESPEN) recommends a target intake of 35–40 kcal/kg/day and 1.2–1.5 g/kg/day of protein (34). In patients with sarcopenia and hepatic encephalopathy, protein restriction is not recommended (161). In fact, protein restriction in liver transplant candidates is associated with higher mortality while on the waitlist (162). Due to impairments in liver function, patients with cirrhosis have inadequate glycogen stores. To counter the accelerated starvation state in these patients, small, frequent meals and a late evening snack consisting of 50 grams of complex carbohydrates are suggested (162,163). Per a 2016 study by Sinclair *et al*., testosterone supplementation may safely increase muscle and bone mass in cirrhotic males with sarcopenia and low testosterone levels (164). However, there is currently no treatment directed at cirrhotic patients with sarcopenia. A 2013 review of sarcopenia in the post-LT period attributed unresolved sarcopenia to use of immunosuppressive agents such as mammalian target of rapamycin (mTOR) and CNIs, which can impair skeletal muscle growth, repeated hospitalizations, renal impairment, and infectious

Table 4 Metabolic equivalent tasks (METs) can be used to assess functional status in liver transplant candidates

METS	Estimated functional capacity
>10	Excellent: rope jumping, rowing, running (>7 mph)
7–10	Good: running (6 mph), circuit training
4–6	Moderate: walking up 2 flights of stairs, walking on level ground at 4 mph, cycling for leisure or commuting
<4	Poor: slow ballroom dancing, walking at 2–3 mph, light house work (cleaning, sweeping)

One MET is considered the resting oxygen consumption of a 40-year-old 70 kg man. Adapted from (118).

complications (165).

Portal venous thrombosis

Obesity and diabetes are highly prevalent in NASH cirrhosis and are well-known risk factors for vascular thrombosis. Additionally, obesity and diabetes are independent risk factors for developing a pre-transplant portal vein thrombosis (PVT) in liver transplant candidates (166,167). According to Agbim *et al.*, NASH transplant recipients with PVT had a 37% increased risk of graft failure and 31% increased risk of overall death when compared with NASH transplant recipients without PVT at the time of transplant. This difference in graft and patient survival was most pronounced in the first 90 days following LT (36).

Recent evidence suggests that NAFLD mechanistically alters coagulation independent of abdominal adiposity and metabolic syndrome (168). Chronic liver steatosis in NASH patients is associated with an increase in the activity of clotting factor VII, plasminogen activator inhibitor-1 activity and antigen and a decrease in tissue-type plasminogen activator (t-PA) activity (169). In patients with NASH, factor VIII levels seem to be higher and pro C levels seem to be lower, leading to an imbalance in coagulation status (170). Stine *et al.* reviewed the data of patients who received LT between January 01, 2003 and December 31, 2012 from the United Network for Organ Sharing organization and found that 6.3% patients receiving LT had PVT and 12.0% of those patients had NASH (171). Montenovo *et al.* and noted that presence of portal venous thrombosis while on the waitlist or at the time of transplant lead to worse patient and graft survival in the post-liver transplant period PVT was also an independent risk factor for being removed from the waitlist (167). Martino *et al.* studied a total of 465 patients and noted that waitlist mortality was higher in patients with NASH compared to other liver diseases but portal venous thrombosis did not affect waitlist mortality (37). A randomized controlled trial proved that a 12-month course of enoxaparin was effective in preventing portal venous thrombosis in patients with cirrhosis and also improved decompensation and survival rates (172). The use of transjugular intrahepatic portosystemic shunt (TIPS) may be a second-line treatment for PVT if anticoagulation fails, however the data is scarce (173).

PVT poses a technical challenge during LT. The extent of portal vein occlusion can lead to further problems in the post-LT period. Restoring portal blood flow to the allograft is essential for successful transplantation and recovery of liver function (174,175).

Immunosuppressants

Post-transplant metabolic syndrome is very common in NASH patients and is accentuated using immunosuppressive agents. Optimization of dose of immunosuppressive agents improve patient and graft survival. Steroid free regimens are known to decrease diabetes, hyperlipidemia, cytomegalovirus infections but no difference in patient and graft survival, renal insufficiency, hypertension, neurological disorders and infectious complications were noted (102). CNI use is associated with diabetes, hypertriglyceridemia and obesity in post-transplant patients (176). Hypertension and hyperlipidemia are more common in patients using cyclosporine compared to tacrolimus (177). Lower tacrolimus trough concentrations within the first month after LT were associated with less renal impairment at 1 year with no significant influence on acute rejection compared to conventional tacrolimus trough levels (178). But tacrolimus is known to increase NASH after liver transplant (179).

Recent systematic review of 12 studies showed prevalence of de novo NAFLD was 26% and prevalence of NASH was 2%. Highest prevalence of de novo NAFLD were found in patients taking tacrolimus (180). Both cyclosporine and tacrolimus regimen use cause increased

risk of cardiovascular events compared to non-cyclosporine regimens (127). Post-transplant deaths, re-transplantation rate was higher in cyclosporine group compared to tacrolimus group (181). The utility of cyclosporine based regimen is of historical interest only. Mycophenolate and mammalian target of rapamycin (mTOR) inhibitors were used to decrease the use of tacrolimus frequently in post-transplant period to decrease metabolic complications (182). Sirolimus-based immunosuppression is associated with a significantly higher risk of NODAT than other immunosuppressants as noted earlier.

Conclusions

Management of NASH in the peritransplant period possesses unique challenges to providers involved in the care of these patients due to its associated comorbidities such as type 2 diabetes, obesity, metabolic syndrome, cardiovascular diseases and CKD. Optimal selection of transplant candidates with NASH involves stringent cardiac evaluation with low threshold for cardiac angiogram particularly in those with high risk CAD history even in the face of normal cardiac stress testing. Pretransplant diabetes is associated with inferior post-operative outcomes and increased resource utilization after LT, and as such a strict control of diabetes using a multidisciplinary approach involving primary care physician, endocrinologist, and dietician combined with a structured weight loss program is of paramount importance for obtaining an optimal outcome in these high-risk patients. Nutritional intervention should be a focus for treating sarcopenia in cirrhotic patients awaiting LT with focus on high protein intake. Frailty is predictor of poor post-transplant outcome, and supervised exercise program should be considered in high risk patients with poor functional capacity. Consideration should be given for early intervention with modification of immunosuppression regimen to protect renal function in those patients with baseline renal dysfunction.

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Footnote

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